

# Giant cell arteritis in patients with systemic sclerosis: a case series

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## Abstract

### Objective

*Giant cell arteritis (GCA) in patients with systemic sclerosis (SSc) is rare, and optimal treatment strategies for this group of patients have not been defined. We aim to describe the first case series of GCA/SSc overlap.*

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### Methods

*A single-institution retrospective study was performed reviewing all patients that had diagnosis codes for both SSc and GCA between January 1, 1996, and December 31, 2020. Demographic characteristic, clinical presentation, diagnostic modality, treatment, and outcome data were abstracted. Diagnosis of both SSc and GCA by a rheumatologist was required for inclusion.*

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### Results

*Eight patients were retrospectively identified, all of which were female. Seven patients fully met both respective ACR/EULAR classification criteria sets. One patient fulfilled GCA criteria and had 8/9 points for SSc criteria plus an oesophagogram which was consistent with clinical diagnosis of SSc. Three patients had a previous history of scleroderma renal crisis (SRC) prior to glucocorticoid initiation for GCA. No episodes of SRC occurred following initiation of glucocorticoids. Three patients were treated with tocilizumab. One patient developed a diverticular perforation while on tocilizumab requiring colonic resection and colostomy, one patient discontinued tocilizumab after a medication-unrelated complication and one patient has remained on treatment and in remission.*

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### Conclusion

*Herein we present the largest single-institution series of patients with a history of GCA and SSc, an uncommon combination. Glucocorticoid treatment for GCA did not precipitate SRC, even in those with prior history of SRC. Further investigation regarding the benefit of tocilizumab in patients with SSc and GCA is required.*

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### Key words

vasculitis, giant cell arteritis, systemic sclerosis, tocilizumab, scleroderma renal crisis

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## Introduction

Giant cell arteritis (GCA) is the most common form of primary vasculitis in patients  $\geq 50$  years old, and glucocorticoids (GCs) have been the historic mainstay of therapy (1-4). Its presentation with concomitant rheumatic diseases is rare. GCA in patients with diagnosis of systemic sclerosis (SSc) is limited to case reports (5). The use of high-dose GC therapy in SSc patients is controversial and requires careful monitoring due to concern of scleroderma renal crisis (SRC) (6-8). The objective of this study was to identify a series of patients with diagnosis of GCA and SSc and describe their clinical features, treatment response, and outcome.

## Methods

A single-institution retrospective study was performed reviewing all patients that had at least one diagnosis code for both SSc and GCA between January 1, 1996, and December 31, 2020. Medical records were manually reviewed, and data were abstracted regarding demographic characteristics, clinical presentation, diagnostic modalities, treatments, and outcomes. Diagnosis of both SSc and GCA by rheumatologist was required for inclusion. Number of American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria met for 2013 SSc criteria and 2022 GCA criteria were documented (9, 10). This study was reviewed and approved by the Mayo Clinic institutional review board (IRB 21-012039) and was conducted in accordance with ethical principles of human research as outlined in the Declaration of Helsinki.

## Results

### Scleroderma

A total of eight patients (100% female) with diagnosis of GCA and SSc were retrospectively identified; 6/8 patients were diagnosed with SSc before GCA. In patients with SSc diagnosis preceding GCA, mean (standard deviation, SD) time from SSc diagnosis to GCA diagnosis was 19.6 (15.7) years. The mean (SD) age at SSc diagnosis was 60.5 (17.1). All patients were clinically diagnosed as SSc by a trained rheumatologist with 7/8 patients fulfilling 2013

ACR/EULAR classification criteria for SSc. The patient that did not fully meet classification criteria had a score of 8/9 plus an esophagogram that was consistent with SSc. Clinical features of SSc, disease subtypes, treatments and outcomes are further noted in Table I.

All patients at some point of the disease used either a calcium channel blocker (CCB), angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB). Two patients were using an ACE inhibitor before SSc diagnosis for essential hypertension. Seven patients were using either a CCB or an ACE/ARB medication at the time of GCA diagnosis when high-dose GCs were initiated (3/7 CCB+ACE/ARB, 2/7 ACE/ARB only, 2/7 CCB only).

Three patients had a documented history of scleroderma renal crisis (SRC) prior to GCA diagnosis. Only one (case no. 2) had a positive anti-RNA polymerase III. This patient (case no. 2) did develop an episode of hypertensive urgency (blood pressure 200/140 mm Hg) four days after the initiation of high-dose GCs following the diagnosis of GCA. This, however, occurred while remaining on an ACE inhibitor but after having transiently held hydrochlorothiazide due to reduced oral intake. Reintroduction of the thiazide diuretic resulted in blood pressure normalisation without any further hypertensive episodes and no end-organ damage or features of SRC were observed.

During the course of disease, four patients developed interstitial lung disease (ILD) [cases no. 1-4] and one patient developed pulmonary hypertension [case no. 1]. At last visit all patients who had had ILD were deceased, of which two of the deaths were felt due to SSc complication. Among the patients alive at last follow up, all four patients were considered clinically stable on treatment (Table I).

### Giant cell arteritis

Two of the eight patients were diagnosed with GCA before SSc. The mean (SD) time from GCA diagnosis to SSc diagnosis was 1.8 (1.1) years. The mean (SD) age at GCA was 74.8 (6.9) years. Following diagnosis of GCA the length

Competing interests: K.J. Warrington received support from Eli Lilly and Kiniksa for clinical trials in GCA. The other authors have declared no competing interests.

**Table 1.** Clinical features of SSs, GCA, disease subtypes, treatments and outcomes.

Case	Systemic sclerosis				Giant cell arteritis			Outcomes			
	Age SSs DX	SSs subtype, Sx & Serology	Tx for SSs prior to GCA Dx	Hx SRC	Age GCA Dx	Method GCA Dx	GCA Sx & IMs at Dx	Initial GC dose	GCA GC-sparing agents used	Complications	Status DX
n. 1	57	lcSSc CC, DU, GERD, RP, SD, TE, ANA, Anti-Scl-70	CCB, EIRA, HCQ, PDE <sub>5</sub> -I	Yes, 1 episode	66	Clinical	HA, PMR, ST CRP: 22 mg/L ESR: 55 mm/h	40mg	None	<u>GCA</u> : None <u>SSc</u> : pHTN, ILD	<u>Deceased</u> : Complications of Scleroderma
n. 2	45	dcSSc DU, GERD, IA, RP, SD, TE, Anti-RNA Pol III	Penicillamine (D/C AE), HCTZ, ACEI	Yes, 1 episode	73	Clinical	HA, JP, PMR, ST, VS CRP: 66 mg/L ESR: 46 mm/h	40mg	None	<u>GCA</u> : GC-related: IHG, OP & VCFs <u>SSc</u> : ILD, severe HTN episode without SRC	<u>Deceased</u> : Cause of death N/A
n. 3	43	dcSSc CC, DU, ED, GERD, RP, SD, TE, Anti-Scl-70	CCB	No	86	Biopsy	HA, JC, JP, PMR, VS CRP: N/A ESR: 73 mm/h	40mg	None	<u>GCA</u> : None <u>SSc</u> : ILD, hand contractures, finger autoamputations.	<u>Deceased</u> : Ruptured sigmoid volvulus
n. 4	81	dcSSc ED, GERD RP, SD, TE, Anti-RNA Pol III	None (SSc Dg after GCA)	No	78	Clinical	HA, PMR, ST, FE, NS CRP: N/A ESR: 60 mm/h	60mg	None	<u>GCA</u> : N/A <u>SSc</u> : ILD, severe dysphagia.	<u>Deceased</u> : Failure to thrive due to severe dysphagia.
n. 5	76	lcSSc GERD, RP, SD, TE, ANA, ACA	CCB	No	79	Biopsy	JC, PMR, VS CRP: 86.8 mg/L ESR: 72 mm/h	60mg	TCZ	<u>GCA</u> : PVFD <u>SSc</u> : None	<u>GCA</u> : Remission, on TCZ 4mg/kg IV q4wks. <u>SSc</u> : Stable, on CCB, PPI
n. 6	34	lcSSc DU, GERD, RP, SD, ANA	PDE <sub>5</sub> -I, AZA, CYC, HCQ, LEF, MTX, MMF	Yes, 1 episode	63	Biopsy + LV Imaging	HA, PMR, VS CRP: 22 mg/L ESR: 43 mm/h	60mg	1 <sup>st</sup> line: TCZ (D/C AE) 2 <sup>nd</sup> line: LEF (D/C AE) 3 <sup>rd</sup> line: MTX	<u>GCA</u> : Diverticular perforation 2ry to TCZ, PVFD, adrenal insufficiency 2ry to GCs. <u>SSc</u> : Hand contractures	<u>GCA</u> : clinically stable on prednisone 15mg + MTX <u>SSc</u> : stable, PDE <sub>5</sub> -I
n. 7	69	lcSSc DU, ED, GERD, IA, RP, SD, TE, ACA	HCQ, CCB, ACEI	No	75	Biopsy	HA CRP: N/A ESR: 40 mm/h	60mg	None	<u>GCA</u> : None. <u>SSc</u> : None.	<u>GCA</u> : Remission, off Tx <u>SSc</u> : Stable, lost to F/U 2013 (but using HCQ, CCB, PPI)
n. 8	79	lcSSc GERD, RP, TE, ANA, ACA	None (SSc Dg after GCA)	No	78	Clinical, LV imaging for relapse (aortitis)	HA, PMR, JC CRP: N/A ESR: 103 mm/h	40mg	TCZ	<u>GCA</u> : Aortitis (relapse), GC-related OP. <u>SSc</u> : None	<u>GCA</u> : Remission, off Tx <u>SSc</u> : Stable, on CCB

ACA: anti-centromere antibody; ACEI: angiotensin converting enzyme inhibitor; ANA: antinuclear antibody; AZA: azathioprine; CCB: calcium channel blocker; CRP: C reactive protein; CYC: cyclophosphamide; D/C AE: discontinued due to adverse event(s); dcSSc: diffuse cutaneous systemic sclerosis; DU: digital ulcerations; EIRA: endohelmin 1 receptor antagonist; ED: oesophageal reflux disease; HA: headache; HCQ: hydroxychloroquine; HCTZ: hydrochlorothiazide; IA: interstitial lung disease; IHG: inflammatory markers; JC: jaw claudication; JP: jaw pain; LEF: leflunomide; lcSSc: limited cutaneous systemic sclerosis; LV: large vessel; MTX: methotrexate; MMF: mycophenolate mofetil; N/A: not available; NS: night sweats; OP: osteoporosis; PDE<sub>5</sub>-I: phosphodiesterase 5 inhibitor; pHTN: pulmonary hypertension; PMR: polymyalgia rheumatica; PPI: proton pump inhibitor; PVFD: permanent visual field defect; RP: Raynaud's phenomenon; SD: sclerodactyly; SRC: scleroderma renal crisis; SSs: systemic sclerosis; ST: scalp tenderness; TCZ: tocilizumab; TE: telangiectasia(s); Tx: treatment; VCFs: vertebral compression fractures; VS: visual symptoms.

of observance for the eight patients averaged 5.2±4.2 years. GCA-related symptoms at time of diagnosis are listed in Table I. Diagnosis of GCA was based on positive temporal artery biopsy (TAB) in three cases, TAB plus positive large vessel imaging in one case, and clinically diagnosed in the remaining 4 cases. Of the four clinical diagnoses, one patient (case no. 8) had subsequent large-vessel imaging on relapse demonstrating aortitis. All patients fulfilled 2022 ACR/EULAR GCA classification criteria. GCs were started in all patients following GCA diagnosis; four patients at 40 mg/day oral prednisone and the remaining on 60 mg/day.

Following GCA diagnosis, three patients received tocilizumab. One patient had no tocilizumab-associated complications and remained on tocilizumab, off GCs, and in remission at last follow-up. One patient (case no. 6) developed a diverticular perforation requiring bowel resection and colostomy while on tocilizumab resulting in the transition to oral leflunomide (stopped due to hives) and then subsequently to methotrexate. Of note, this patient had a history of diverticulosis but no prior history of diverticulitis nor known SSc-associated intestinal dysmotility. One patient (case no. 8) received 4 doses of tocilizumab, which was then stopped for a non-GCA/non-SSc associated surgery and did not restart.

At last follow-up, among the four living patients, two (cases no. 7, 8) achieved GCA remission and were off treatment, and two (cases no. 5, 6) were in remission on treatment.

## Discussion

This series comprises the largest single-institution description of patients with GCA and SSc. While ANCA-associated vasculitis has been described in patients with SSc, occurring in up to 1–2% of patients with SSc, the presence of GCA in SSc is exceptional (11). Given the low frequency of occurrence of concomitant GCA and SSc in the same patient, it is perhaps more likely these aetiologies occurred by chance rather than due to etiologic overlap. In this series, no episodes of SRC developed after initiation of high-dose GC

for GCA. Prior studies have associated moderate-to-high dose GCs in SSc patients with SRC, and if used, suggest patients have careful blood pressure and renal function monitoring (6-8). Although an association with SRC and GCs has been noted, studies evaluating risk have acknowledged that the causal relationship between GC therapy and SRC is difficult to assess, particularly since SRC has been reported more often in certain disease subsets, such as early diffuse cutaneous SSc with poor prognostic factors, who were receiving additional immunosuppressants, nephrotoxic agents, and in several cases, undergoing stem cell transplantation (6, 7). Given the fact that GCA is a medical emergency for which prompt initiation of GCs remain a key initial treatment, patients with history of SSc with or without SRC pose a challenge and the amount of GCs used in this unique subset should be determined based on a case-by-case risk *versus* benefit assessment. Though few in number, this report highlights that use of GCs in patients with SSc and GCA can be performed safely with low risk for development of SRC.

Seven of eight patients were taking at least one anti-hypertensive agent at the time of GCA diagnosis and initiation of high-dose GCs. It is possible that use of anti-hypertensive agents exhibited a potential protective effect reducing the development of SRC in these patients. It is noteworthy, however, that large database studies evaluating the risk of SRC in patients with SSc noted that pre-existing use of ACE inhibitor increased the risk for SRC, independent of arterial hypertension, while CCB and ARB did not influence the hazard ratio for SRC (12). The protective role of baseline antihypertensive treatment is uncertain and the size of the current series is insufficient to draw conclusions; however, current standard-of-care in SRC suggests use of ACE inhibitors only as treatment, and use as prophylaxis is not recommended (8). To our knowledge, this is the first report of patients with both GCA and SSc that were managed with tocilizumab. At current, tocilizumab is the only FDA-approved biologic agent for both

GCA and SSc-associated lung fibrosis (13, 14). The majority of cases in the current report were diagnosed prior to the FDA approval of tocilizumab for both diseases, therefore it was used only in three patients. The concern of SRC raises the question whether tocilizumab monotherapy without adjunct GC or tocilizumab plus accelerated or ultra-short GC taper are viable alternatives in patients with concomitant GCA and SSc. These strategies have been explored mainly in the context of large-vessel GCA without concomitant SSc, thus leaving the safety and efficacy of tocilizumab monotherapy in the GCA-SSc entity unexplored and requiring further evaluation (15).

Bowel perforation is a known yet uncommon side effect of tocilizumab and occurred in one patient in this case series (16). Bowel perforation, however, has also been associated with SSc-related intestinal dysmotility and/or intestinal pseudo-obstruction, a known yet uncommon complication seen in some SSc patients (17). While the level of risk is not fully understood and cannot be quantified based on the size of the current series, it may be reasonable to consider avoiding use of tocilizumab in patients with GCA and SSc with prior history of diverticulosis/diverticulitis, intestinal perforation, intestinal surgery, or SSc-related intestinal dysmotility.

In conclusion, this report highlights the largest series of patients with GCA and SSc. In this series, GCs did not appear to convey an increased risk of SRC. Outcomes for patients treated with tocilizumab were mixed and require further evaluation in this unique patient subset.

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